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DOI: <https://doi.org/10.1016/j.ctrv.2012.05.008>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-64663>

Journal Article

Accepted Version

Originally published at:

Laperriere, N; Weller, M; Stupp, R; Perry, J R; Brandes, A A; Wick, W; van den Bent, M J (2013). Optimal management of elderly patients with glioblastoma. *Cancer Treatment Reviews*, 39(4):350-357.

DOI: <https://doi.org/10.1016/j.ctrv.2012.05.008>

Optimal Management of Elderly Patients with Glioblastoma

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Abstract

Median age at diagnosis in patients with glioblastoma (GB) is slowly increasing with an aging population in Western countries, and was 64 years in 2006. The number of patients age 65 and older with GB will double in 2030 compared with 2000. Survival in this older cohort of patients is significantly less than seen in younger patients. This may in part be related to more aggressive biology of tumor, reduced use of standard management approaches, increased toxicity of available therapies, and increased presence of comorbidities in this older patient population. Limited data do support the use of more extensive resection in these patients. Randomized data support the use of post-operative radiotherapy (RT) *versus* supportive care, but do not demonstrate a benefit for the use of the standard 6 weeks course of RT over hypofractionated RT given over 3 weeks. Preliminary data of randomized studies raise the possibility of temozolomide alone as an option for these patients. The use of 6 weeks of RT with concurrent and adjuvant temozolomide has been associated with reasonably good survival in several uncontrolled small series of selected older patients; however, this better outcome may be related to the selection of better prognosis patients rather than the specific therapy utilized. The current National Cancer Institute of Canada (NCIC) and European Organization for Research and Treatment of Cancer (EORTC) CE.6/26062/22061 randomized study of short course RT with or without concurrent and adjuvant temozolomide will help determine the optimal therapy for this older cohort with currently available therapies.

Introduction

Glioblastoma (GB) is a uniformly fatal illness associated with a median survival of less than one year. For the past several decades, post-operative radiotherapy (RT) had been the mainstay of therapy as the only treatment to significantly prolong survival following surgery.¹ The European Organization for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada (NCIC) randomized study of RT alone or RT with concurrent and adjuvant temozolomide demonstrated a significant improvement in median survival from 12.1 to 14.6 months, and an improvement in 2-year survival from 10% to 26%, respectively.^{2,3} Patients age 65 or older now form half of all patients with GB and they fare considerably less well than their younger counterparts, with a population based median survival of approximately 6 months.⁴⁻⁶ The role of chemotherapy in addition to RT in the elderly has remained controversial. The RT dose used in the EORTC–NCIC CTG study was 60 Gy in 30 fractions and the study population was restricted to age 18 to 70 with an ECOG performance status of 0–2. Exploratory sub-group analysis of

the results from this study revealed a persistent but diminishing benefit from the addition of temozolomide with increasing age (Table 1).⁷ This preliminary analysis served as the basis for the current ongoing NCIC CTG-EORTC randomized trial of the use of temozolomide in elderly patients with GB.(7) Subsequent publication of the EORTC–NCIC CTG study with longer follow up did in fact demonstrate an improvement in survival in the older age group (60-70).(2)

Table 1: Hazard ratio by age group in the EORTC–NCIC trial demonstrating a diminishing benefit of temozolomide with increasing age⁷

Age, years (number of patients)	Hazard ratio	P value
< 50 (171)	0.5	0.001
50-60 (220)	0.63	<0.05
61-65 (114)	0.64	0.096
66-70 (83)	0.78	0.340

The optimal management of older patients with GB beyond RT remains unresolved. Older age is often associated with increased toxicity to many drugs, possibly related to increased vulnerability of multiple organ systems that have experienced a reduction in functional reserve, and resulting in increased likelihood of myelosuppression, mucositis, neurotoxicity and cardiotoxicity.⁸ Increased toxicity in patients 65 or older has also been documented with the use of biologic agents. Retrospective analysis of two trials for advanced lung cancer with erlotinib and bevacizumab revealed significantly higher levels of toxicity in the older patients compared with the younger patients in those studies.^{9,10} The risk and degree of radiation-related neurotoxicity has also been noted to increase with age.^{11,12}

Lawrence and colleagues from the Radiation Therapy Oncology Group (RTOG) performed a retrospective review of neurotoxicity of acute and late grade ≥ 3 neurotoxicity in 2,761 patients from 14 prior RTOG trials in high-grade gliomas from 1983 to 2003. All patients had received either chemotherapy (83%) or a biologic agent (17%) during RT (median dose 60 Gy). The incidence of acute neurotoxicity (defined as grade 3 or greater events by RTOG Acute Morbidity Scoring Criteria occurring within 3 months of starting therapy) was associated with older age, poor performance status, aggressive surgery, pre-existing neurological dysfunction, poor mental status, and twice-daily radiation on univariate analysis. Acute neurotoxicity was associated with poorer median survival (7.8 versus 11.8 months).¹³

Of note, older patients have often been excluded from participation in clinical trials and as a result of limited controlled data, may receive overly aggressive or inadequate reduced-intensity treatment. It is becoming increasingly important that future trials either focus on older patients or include older patients, as they currently represent 50% of all patients with GB, and will soon represent the majority of patients with GB. In view of the poor outcomes associated with increasing age, quality of life becomes an increasingly important issue in this population of patients in addition to survival; unfortunately this is poorly documented in the current published retrospective series, and will only come from prospective ongoing trials.

Epidemiology

An important predictor of outcome in GB is age. Recent large population-based cohorts of patients with GB demonstrated a marked decrease in median survival with increasing decade of age, and in particular showed a median survival of approximately 6 months in patients age 65 and older.^{4-6,14}

With an aging population and improved diagnostic tools the incidence of GBM has been steadily increasing over the last 20–30 years, and this increase is almost exclusively observed in patients older than 70 years.¹⁵ Median age at diagnosis for GB was 64 years over the years 2002–2006 from a large United States (US)-based cancer registry.¹⁶ In the US, the number of adults aged 65 or older increased from 25 million in 1980 to 35 million in 2000, and is expected to increase to 72 million by 2030.^{17,18} This “silver tsunami”, as characterized by the US National Institute on Aging, will lead to at least a doubling of cases of GB in patients age 65 or older over the next two decades, and this age group will account for two-thirds of all cases of GB by 2030.^{8,19} Similar demographic data exists for most Western countries, including Canada, Australia, and most European nations.

Patterns of Care

GB arising in older patients tends to present with a relatively short symptomatic phase of a few weeks and tends to rapidly impair cognition and functional independence.²⁰ In view of its aggressive biology, short survival, limited efficacy of available therapies, and common presence of comorbidities in this population, older patients with GB are less likely to receive standard therapy than younger patients. In a population-based review of the management of 3,279 adult patients with GB in Ontario, Paszat and

colleagues documented that with the odds ratio set at 1.00 for the age group 60–69, patients aged 70–79 and those aged ≥ 80 years had an odds ratio of 0.77 and 0.25 for total/subtotal resection respectively. Similarly those two age groups had an odds ratio of 0.40 and 0.13, respectively, for having received any radiotherapy.⁶ Similar results were reported from three other population-based reviews and are in part felt to be related to the general poorer condition of older patients with newly diagnosed GB as well as an increasing incidence of comorbidities in this older cohort.^{1,5,6,14} In a review by Kita and colleagues, best supportive care only was increasingly the treatment given to older patients: in those aged 55–64, 65–74, and ≥ 75 years it was given in 27%, 44%, and 75% of patients, respectively.⁵ In addition, the report on the Ontario experience documented that the proportion of patients spending 100% of their survival time in hospital in the age groups 60–69, 70–79, and ≥ 80 increased from 21.9%, to 38%, and 49.5%, respectively, so that clearly the quality of survival decreases with increasing age in a population-based review.⁶ A population-based review of 4,137 patients with GB aged 65 or older documented that age was the most significant predictor for resection, RT, or chemotherapy, and that advancing age was associated with a decreasing use of all three modalities.⁴ The same study showed that the presence of comorbidities was also associated with a decreasing likelihood of receiving RT and chemotherapy. In a population-based review of 715 cases of GB in the Canton of Zurich, Switzerland, that were diagnosed between 1980–1994, Kita et al. noted that only 25% of patients aged 75 or older had undergone surgery (gross total or subtotal resection) and/or RT as compared with 47% of patients aged 65 or older and 82% of patients aged <65 years.⁵ A population-based review of 1,753 patients with GB older than 65 years also documented lower rates of surgical resection and RT in patients aged 75 years or older compared with patients aged 66–74.¹⁴

There are also concerns about an increased likelihood of toxicity from treatment in elderly GB. Sijben et al. reported a 42% rate of grade 3 or 4 toxicity (grade 3: 1 fatigue, 1 liver enzyme elevation, 1 pneumocystis pneumonia; grade 4: 1 syndrome of inappropriate anti-diuretic hormone release, 1 urosepsis, 3 myelosuppression) in 19 patients aged 65 or older who received 6 weeks of RT with concurrent and adjuvant temozolomide. This was a significantly higher rate than in the EORTC–NCIC randomized study, where the comparable rate was 16% in 287 patients aged 18–70.^{3,21} Grade 3–4 hematologic toxicity occurred in 28% of a series of 32 consecutive patients aged 70 or older treated with 6 weeks of RT with concurrent and adjuvant temozolomide.²² Grade 3–4 hematologic toxicity occurred

in 28% of a series of 43 patients aged 70 or older treated with hypofractionated RT (30 Gy in 6 fractions over 2 weeks) followed by adjuvant temozolomide.²³

In summary, population-based data demonstrate an increased likelihood of biopsy, a lower rate of resection, a lower use of RT and chemotherapy, and a higher incidence of toxicity. These patterns of care were related to older age and the presence of increased comorbidities within the population of elderly patients.

Prognostic Factors

As seen with the overall population, age, performance status, tumor size, and extent of resection remain important prognostic factors in older patients with GB.^{4,21,24-27} The RTOG recursive partitioning analysis from 1,578 patients entered in three RTOG malignant glioma trials did not include patients older than 70 years.²⁸ Lamborn and colleagues undertook a recursive partitioning analysis of prognostic factors for 832 patients with GB entered on non-brachytherapy trials with planned adjuvant chemotherapy.²⁹ They identified four risk groups and the highest risk group included all patients older than 65 years, independent of performance status or extent of surgical resection, and patients between 40 and 65 years with either Karnofsky performance status (KPS) <80 or biopsy only.

A major molecular prognostic factor identified from the EORTC–NCIC trial in younger patients with GB was the methylation status of *O*⁶-methylguanine-DNA methyltransferase (*MGMT*) gene promoter, which identifies patients who may benefit from the use of temozolomide.³⁰ There have been several recent reports of the rate of *MGMT* promoter methylation in elderly patients and its effect on survival (Table 2). Piccirilli et al. report on a cohort of 22 patients aged 80 or older with GB: 13 (59%) patients had methylation of the *MGMT* gene promoter, and *MGMT* promoter methylation was associated with a mean overall survival (OS) of 17.9 versus 7.7 months for the 9 patients without *MGMT* methylation ($p = 0.0006$).³¹ Sijben et al. reported that the *MGMT* gene promoter was hypermethylated in 13/29 (45%) cases in their series of 39 patients aged 65 or older.²¹ Median OS and median progression-free survival (PFS) times were not statistically different for methylated (7.4 and 4.5 months, respectively) and unmethylated (7.3 and 5.5 months, respectively) cases.²¹ Gerstner et al. found that 37/64 (57.8%) patients aged 70 or older with GB had methylation of the *MGMT* promoter, similar to the rate of 44.7% seen in the EORTC–NCIC trial.^{24,30} Age, extent of resection, KPS, and *MGMT* promoter methylation were associated with a reduced hazard for progression and death in a multivariate Cox model in this cohort of 64 elderly patients.²⁴ Brandes et al. reported methylation in 16/37 (43%) of a series of 58 patients aged 65 or older (median age 68, range 65–82).³² Hypermethylated patients had a median PFS of 22.9 months and median OS was not reached, while in unmethylated cases the respective results were 9.5 and 13.7

months. PFS and OS were significantly different by *MGMT* status. The overall outcome in this patient group was strikingly better than in all other studies in this age population, suggesting patient selection with better prognostic factors as a possible source of bias in this data set. Minniti and colleagues in Rome reported on 83 patients aged 70 or older with GB where the *MGMT* promoter was methylated in 42 (50.6%) patients and unmethylated in 41 (49.4%) patients.³³ Median PFS and OS were 10.5 and 15.3 months, respectively, for the methylated cases and 5.5 and 10.2 months, respectively, for the unmethylated cases. The largest study was presented at the ASCO Meeting 2011 by the German Glioma Network. In a prospective analysis of 233 patients aged 70 or more, the rate of *MGMT* promoter methylation was 57.5%, and OS, but not PFS, was longer in patients with *MGMT* promoter methylation.³⁴

Table 2: Studies documenting *MGMT* methylation status in elderly patients with GB

Authors	Year	N	Age (yr)	Methylation Status	mPFS (mo)	mOS (mo)
Piccirilli et al ³¹	2006	22	≥80	59% methylated	NA	17.9
				41% unmethylated	NA	7.7
Sijben et al ²¹	2008	29	≥65	50.6% methylated	4.5	7.4
				49.4% unmethylated	5.5	7.3
Gerstner et al ²⁴	2009	64	≥70	57.8% methylated	10.8	16.1
				42.2% unmethylated	5.7	8.6
Brandes et al ³²	2009	37	≥65	40.7% methylated	22.9	NR
				59.3% unmethylated	9.5	13.7
Minniti et al ³³	2011	83	≥70	50.6% methylated	10.5	15.3
				49.4% unmethylated	5.5	10.2
Weller et al ³⁴	2011	233	≥70	57.5% methylated	5.2	8.4
				42.5% unmethylated	4.7	6.4

yr = year; mPFS = median progression free survival; mOS = median overall survival; NA = not available;

NR = not reached; NA* = not reported, but reported to not be different between methylated and unmethylated cases

To conclude, *MGMT* promoter methylation, a favorable prognostic factor, is altogether as common in the elderly despite their overall worse outcome and are associated with an accompanying positive prognostic effect. In contrast, another novel molecular marker in gliomas, isocitrate dehydrogenase 1 (IDH) mutation, is age-correlated. IDH mutations are very common, in the range of 50–80% in gliomas of

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grades II/III, but rare in GB, in the range of 10%.³⁵ Across all types of gliomas, IDH-1 mutated tumors show a less malignant course. Since IDH mutations are virtually absent in GB of the elderly and also in anaplastic astrocytomas in the elderly, the age-dependent distribution of IDH mutations may partially explain a small portion of the negative impact of age in malignant gliomas and the similar survival seen in cases of anaplastic astrocytoma and GB in the elderly.³⁶

In summary, older age is a dominant treatment-independent adverse prognostic factor seen in both population-based and institutional reports. Performance status, tumor size, and extent of resection remain important prognostic factors in older patients with GB. With respect to *MGMT*, most reports demonstrate similar rates of methylation of the *MGMT* gene promoter and an accompanying positive prognostic effect in older patients, and the absence of IDH mutation, a positive prognostic marker.

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Surgery

Vuorinen and colleagues in Finland performed a very small randomized study (30 patients) of stereotactic biopsy *versus* craniotomy and resection of the tumor in patients aged 65 or older with radiologically apparent malignant glioma on their imaging.²⁶ Nineteen were confirmed to have GB and 11 had anaplastic astrocytoma; median survival was 5.7 months for craniotomy and resection versus 2.8 months for biopsy. Although randomized data, the value of this study is limited by the small number of patients and dissimilar risk factors in the randomized groups, which very likely contribute to the sizable difference in outcome.

Investigators from Johns Hopkins assessed surgery in 205 consecutive patients aged 65 or older who underwent surgery (n = 133) or needle biopsy (n = 72), respectively, for GB between 1997 and 2007.³⁷ Amongst these patients, they performed a case control study of 40 patients who underwent surgery and 40 patients who underwent needle biopsy who were matched for the following factors: age, KPS, eloquent involvement, radiation, and temozolomide. Mean age was 73 years for both groups, and perioperative outcomes were not significantly different. Patients who underwent resection had a median survival of 5.7 months versus 4.0 months for a needle biopsy (p = 0.03).

From a subgroup cohort of these patients (129 patients aged > 65 years, mean age 73) they retrospectively assessed outcomes after non-biopsy surgical resections and correlated this with

preoperative factors.³⁸ Significant factors for outcome included KPS, chronic obstructive pulmonary disease (COPD), motor deficit, language deficit, cognitive deficit, and tumor size larger than 4 cm. They noted that patients with 0–1 (Group 1), 2–3 (Group 2), and 4–6 (Group 3) of these factors had statistically different survival times, where the median survival was 9.2, 5.5, and 4.4 months, respectively.³⁸

These few studies of surgery in elderly GB seem to support a modest but significant improvement in survival with a surgical resection as opposed to a biopsy, but with a decreasing benefit from a resection when patients have one or more of the following factors: poorer KPS, neurologic deficits, larger tumor, and patients with COPD.

Radiotherapy

The role of focal brain RT in older patients with GB is no longer disputed. Keime-Guibert and colleagues in France performed a randomized study in 85 patients aged 70 or older (median 73, range 70–85) with a KPS of 70 or higher of post-operative RT (50.4 Gy in 28 fractions) *versus* post-operative supportive care only.³⁹ Median survival was improved from 3.9 months with supportive care only to 6.7 months with RT ($p = 0.002$). Importantly, quality of life and cognitive evaluations were not significantly different between the two arms of the study. In a different approach to understand the value of RT *versus* no RT, a population-based review of 2,836 patients with GB age >70 was undertaken.²⁷ Multivariate analysis showed that RT significantly improved cancer-specific and overall survival after adjusting for surgery, tumor size, gender, ethnicity, and age at diagnosis.

In view of the limited survival in elderly GB, there have been several reports of short course RT in relatively small numbers of patients being associated with median survivals in the range of 4–10 months, survivals seemingly very similar to those seen with the 6-week course of treatment.^{40–45}

Eventually, Roa and colleagues in Canada performed a randomized study of short course RT (40 Gy in 15 fractions in 3 weeks) *versus* standard RT (60 Gy in 30 fractions in 6 weeks) in 100 patients aged 60 or older and a KPS of 50 or higher.⁴⁶ Median survivals were 5.6 months for the 3-week course of RT and 5.1 months for the 6-week course of RT ($p = 0.63$). An increase in post-RT steroid dosage was required in 49% of patients who received the standard 6-week course of RT as compared with 23% of patients who received the 3-week course.

In terms of the timing of RT, there would be some concern for extended delays in initiating RT in this elderly population with aggressive disease and limited survival, particularly in the group of patients who have undergone a biopsy only. A population-based review of 1,375 patients with GB aged 65 or older was undertaken where 1,079 patients underwent resection and 296 patients underwent biopsy.⁴⁷ It was noted that 95% of patients had begun RT within 37 days (essentially 6 weeks) of their surgery, and that the median start date was 16 and 10 days post surgery for resected and biopsied patients, respectively. Waiting time for initiation of RT was not a prognostic factor in both the univariate and multivariate analyses. The authors concluded that as long as patients begin RT within the time frame examined in this population-based study (6 weeks), there should be no detrimental effect on survival. Clearly this was a retrospective study, and one must interpret this result with caution.

RT 60 Gy and Concurrent and Adjuvant Temozolomide

The 5-year analysis of the EORTC–NCIC trial confirmed the benefits of concurrent and adjuvant temozolomide in addition to 6 weeks of RT, and it remains the standard of care for patients with GB aged 18–70 with an ECOG performance status 0–2.² In addition, the prognostic value of the methylation status of the *MGMT* gene promoter was confirmed. So it would seem reasonable to explore this regimen in older patients with GB with a reasonable performance status, particularly in view of recent evidence demonstrating that approximately the same proportion of elderly patients has methylation of the *MGMT* gene promoter, which was associated with a favorable prognosis in 4 of 5 published reports on this issue.^{21,31-34}

Iwamoto and colleagues from Memorial Sloan Kettering reviewed their experience in 394 patients aged 65 or older (median 71.9) with GB treated from 1997 to 2007.²⁵ In this cohort, 107 (27.2%) patients received concurrent temozolomide with 6 weeks of RT and 127 (32.2%) patients received adjuvant temozolomide. Additionally, 42 (10.7%) patients received adjuvant chemotherapy with other agents (33 carmustine, 9 other agents) following the completion of RT. In the multivariate analysis, younger age, better KPS, single tumor, and surgical resection were independent predictors of survival. Because the majority of patients received RT, this data set had a limited ability to examine the effect of RT. In terms of trying to assess the possible benefit of adjuvant chemotherapy, they appropriately excluded patients who were not alive or followed for at least 10 weeks after diagnosis. Comparing 103 patients who received adjuvant chemotherapy to 48 who were only followed after RT, there was a 55% decrease in

the risk of death after adjusting for age, KPS, extent of resection, and number of lesions. There was no benefit found with the addition of concurrent temozolomide in this series. They also looked at time trends in terms of survival, as the majority of patients received concurrent and adjuvant temozolomide from 2005 onwards. When comparing survival between the three eras of diagnosis of 1997–1998, 1999–2004, and 2004–2007, the unadjusted hazard ratio was 1.0 for all three time spans ($p = 0.89$). There was thus no improvement in survival following the introduction of temozolomide into therapy for the latest era, which appears to be at odds with the positive effect of the use of adjuvant chemotherapy in their data set, demonstrating the limited reliability of retrospective approaches in this context. Detailed toxicity or quality of life data were not available from this report.

Similarly, a retrospective review of the experience at the Cleveland Clinic of the management of 206 cases of patients with GB age 70 and older over the years 1979-2007 yielded similar favorable prognostic factors of better performance status, any surgery beyond biopsy, radiation therapy and chemotherapy in a multivariate analysis.(61)

There have been several small, uncontrolled, retrospective reports detailing the possible benefits and tolerability of the use of concurrent and adjuvant temozolomide with 6 weeks of RT in older patients with GB.^{21,22,32,48-51} These reports compare their results to historical controls or to the results of older reports in older patients with GB, with no accounting for the distribution of significant prognostic factors between these groups. Clearly the favorable outcomes in these reports could be related to the selection of patients with better prognostic factors and not related to more aggressive therapy with the full 6 week course of RT with concurrent and adjuvant temozolomide. A few of these reports caution about the use of this 6-week course of chemo-RT in this elderly population in relation to an increased incidence of grade 3 or 4 hematologic toxicity and to a greater incidence of neurotoxicity.^{21,22,32}

The role of concomitant and adjuvant temozolomide in the elderly remains to be clarified, and the apparently improved survival in some uncontrolled series may in fact be related to the selection of patients with better prognostic factors.

Temozolomide Only

In view of the generally poor results seen with any approach in the older populations with GB, and the increased neurotoxicity seen with cranial RT, investigators have explored the use of temozolomide alone in elderly GB patients. There is also an accessibility issue related to RT in this population: eliminating the need of having to travel to a RT centre on a daily basis for 2–6 weeks in a population that is more disabled from the disease than are younger patients could potentially be a major benefit, particularly for those with a poorer performance status or for patients living in rural areas.²⁰

Glantz and colleagues reported on a cohort of 86 consecutive patients with GB aged 70 or older who were offered either temozolomide (5 day schedule every 28 days) or standard RT (60 Gy in 1.8 Gy daily fractions).⁵² Median survival times for the temozolomide (32 patients) and RT (54 patients) groups were 6 months and 4.1 months, respectively, and the 1-year survival rates were 11.9% and 9.3%, and were not statistically significantly different. Age, performance status, and extent of resection were similar in the two groups.

Chinot et al. reported on a series of 32 consecutive patients aged 70 or older (median 75, range 70–81) who were treated with the 5-day regimen of temozolomide.⁵³ Median OS was 6.4 months. Grade 3 or 4 thrombocytopenia and neutropenia toxicity occurred in 6% and 9% of patients respectively.

Chamberlain reported on 15 consecutive patients aged 70 or older (median 79, range 73–87) with GB managed with temozolomide 42 days on, 14 days off (75 mg/m²).⁵⁴ Median OS was 6 months and 4/15 (27%) patients developed grade 3 myelosuppression. Laigle-Donadey and colleagues from France retrospectively analyzed all patients with GB who were eligible for the randomized study of RT versus supportive care in France³⁹ who refused to participate and were treated with temozolomide only (5 days every 28 days regimen, 150–200 mg/m²).⁵⁵ Thirty-nine patients met the eligibility criteria of age 70 or older (median 75, range 70–83) and a KPS of 70 or higher. Median OS was 36 weeks for the whole group and 8 (21%) grade III/IV toxicities (seven hematologic, one gastrointestinal) were seen.

Gallego Perez-Larraya and colleagues reported on 70 elderly patients (median 77) with a poor performance status (KPS of <70, median 60%) who were managed with a 5-day regimen of temozolomide only at a dose of 150–200 mg/m².⁵⁶ Grade 3 to 4 neutropenia and thrombocytopenia occurred in 13% and 14% of patients, respectively. Median PFS was 3.9 months and median OS was 5.8 months, comparable to other reports of elderly patients with a better performance status receiving

radiotherapy. Importantly, an improvement in KPS status of at least 10 points was observed in 33% of patients, allowing some independence in daily activities with a KPS of $\geq 70\%$ in one fourth of the patients. These results clearly indicate that the frequent nihilistic approach to elderly patients should be revisited, and that quality of life at least for a short time can be obtained in a substantial fraction of patients.

There are now five uncontrolled series reporting the use of temozolomide only in older patients with GB, which was well tolerated and associated with a median survival comparable with that seen with the use of RT only in this population.

Randomized Studies of Alternative Approaches

There were preliminary reports of two randomized studies in elderly patients with malignant gliomas reported at the Annual Meeting of the American Society for Clinical Oncology (ASCO) in 2011. Detailed publications are not yet available.

The Neurooncology Working Group (NOA) of the German Cancer Society NOA-08 trial compared standard postsurgical partial brain fractionated RT at a dose of 54–60 Gy in 6 weeks to temozolomide 100 mg/m² in a one week on/one week off schedule in patients with anaplastic astrocytoma or GB who were 65 years or older with a KPS ≥ 60 .⁵⁷ The primary endpoint was median OS. Overall, 412 patients were randomized and 373 patients were included in an event-driven intention-to-treat analysis at 55% of events; median OS was 9.6 months for the RT arm and 8.0 months for the temozolomide arm. The primary endpoint could not be demonstrated in that analysis because the non-inferiority of temozolomide *versus* RT alone was not proven. Moreover, the rate of adverse and serious adverse events was higher in the temozolomide arm in this preliminary analysis.

The Nordic trial enrolled newly diagnosed GB patients aged 60 years or older with ECOG performance status 0–2, who were randomized to either standard RT (60 Gy in 2 Gy fractions over 6 weeks) or hypofractionated RT (34 Gy in 10 x 3.4 Gy fractions over 2 weeks) or 6 cycles of chemotherapy with temozolomide (200 mg/m² day 1–5 every 28 days).⁵⁸ The primary study end point was OS. Three hundred and forty-two patients were randomized and median OS was 8.3 months for TMZ, 7.5 months for hypofractionated RT, and 6 months for 6 weeks of RT. There was no significant difference in OS

between the three treatment arms, with median OS being 8 months for TMZ, 7.5 months for hypofractionated RT and 6 months for 6 weeks of RT ($p = 0.14$).

These two studies yield apparently conflicting results on the comparison of 6 weeks of RT, hypofractionated RT, and temozolomide alone. Further details on PFS and therapy at recurrence will likely help us better understand the significance of the data from these trials and further follow up of both studies may yield additional insights. However, in terms of single modalities, there does not appear to be a detrimental effect with the use of temozolomide only in elderly patients from a survival perspective, but there may be increased toxicity seen with this approach as reported in the German study.

There is a third randomized study in elderly patients with GB currently ongoing. The NCIC-EORTC in collaboration with sites in Australasia (Trans Tasman Radiation Oncology Group and selected sites in Japan) is randomizing patients aged 65 or older with GB and an ECOG performance status of 0–2 to RT of 40 Gy in 15 fractions over 3 weeks or the same RT regimen plus concurrent and adjuvant temozolomide for 12 months.⁷ The trial is designed to accrue 560 patients. In view of the prior data from the Roa study showing similar survival with hypofractionated RT regimens and the standard 60 Gy over 6 weeks regimen, this trial examines the possible additive benefit of combining temozolomide with RT, as was studied in younger patients in the EORTC-NCIC study. Toxicity profile, quality of life, and molecular correlative data are being collected as part of this study. This trial will answer the question as to whether the addition of temozolomide to short-course RT confers a survival advantage over short-course RT alone, and if so, whether it is associated with an acceptable toxicity profile and quality of life experience.

Discussion

Most Western countries are facing a significant demographic shift in the next few decades, with a marked increase in population aged 65 and older to levels never before seen.^{8,17-19} The incidence of GB is significantly higher in older adults, occurring at a rate of 12 cases per 10^5 per year in the 65–74 years age group compared with 3 cases per 10^5 per year in the 45–54 years age group.¹⁶ This will result not only in an increased number of new cases of GB but also raise the proportion of patients aged 65 or older within the overall population of patients with GB.

It is important to note that in population-based reviews of the management of older patients with GB, a substantial proportion of patients do not receive the recommended standard therapy usually offered to younger patients. These facts must be kept in mind when one reviews data of institutional reports on more aggressive approaches in this older cohort of patients, as patient selection of a more favorable sub-group is clearly taking place.

In addition, numerous reports document that the standard 6-week course of RT is more toxic in elderly patients, and that the use of concurrent and adjuvant chemotherapy is also associated with additional toxicity compared with younger patients.^{2,13,21-23} So, these data lead one to question the use of approaches that are currently the standard of care in younger patients where there is more toxicity and less apparent benefit in terms of efficacy and overall survival in this older patient population.

Standardized assessment scales in essential domains as activities of daily living, communication, cognitive function and memory, depression and quality of life would add much needed information about the use of any approach in this patient population.

As a result of their shorter survival and their expected reduced tolerance to full dose RT, there has been a long history of the use of hypofractionated RT approaches in elderly patients.³⁹⁻⁴⁵ Recent randomized studies have documented improved survival with RT *versus* supportive care, and no difference in survival with a 3-week course of RT versus a 6-week course.^{39,46} A larger randomized study (Nordic trial) has also shown the clear absence of any detrimental effect of short-course RT *versus* 6 weeks in patients age 60 or older.⁵⁸ Hence, it would be entirely reasonable in a patient where single modality RT is being considered that short-course RT be the approach over the usual 6-week course that is recommended in younger patients.

In view of the poor survival outcomes seen in this elderly cohort of patients, the use of temozolomide only has been suggested as a possible alternative approach. Several reports of this approach reported median survivals of 6 months, which is similar to that is seen with either short-course or 6 weeks of RT as a single modality.^{52-55,58} The detailed analyses of two recently concluded randomized studies will hopefully define whether temozolomide alone is a reasonable alternative for all or selected subgroups of elderly GB patients.^{57,58}

In terms of approaching this elderly cohort with the standard of care of 6 weeks of RT with concurrent and adjuvant temozolomide, there have been several institutional reports of the uncontrolled use of this approach in elderly patients associated with better median and overall survival than generally seen in reports of elderly patients in general.^{21,24,31-33} It appears that the rate of, and the favorable prognostic effect of *MGMT* gene promoter methylation appears to be similar to that seen in younger patients. However, these favorable results are very likely to be related to the selection of patients with an array of better prognostic indicators, and may not reflect the effect of more aggressive therapy. Some of these reports do indeed report an increased incidence of chemotherapy-related grade 3 or 4 toxicity and neurotoxicity from the 6 week course of RT. Some authors have suggested that selection of patients with methylation of the *MGMT* gene promoter might be a selection criterion for the subgroup of elderly patients who might benefit from 6 weeks of RT with concurrent and adjuvant temozolomide, in an effort to restrict the possible increased toxicity to those that are more likely to benefit from its use.^{21,33} Until there is better agreement on *MGMT* methylation assays and their reproducibility, and more long-term results in prospective patient cohorts, we continue to recommend that *MGMT* methylation assays remain a research tool that does not dictate or influence patient management.⁵⁹ *IDH1* mutations were found in only 16 of 286 (5.6%) patients with GB of all ages in a German translational study, and are generally seen in younger patients, so its absence or rare incidence in older patients with GB may be a minor contributing factor of the poor prognostic effect of age in this disease.^{35,36,60}

So, how is one to approach the management of older patients with GB in the absence of definitive randomized trials for many of the treatment options? As the patterns of care studies demonstrate, clinicians and patients are making choices as to the most appropriate therapy, and only a minority of patients are receiving what is considered the standard of care in younger patients, namely maximal safe resection followed by 6 weeks of RT with concurrent and adjuvant temozolomide.^{4-6,14} Figure 1 is a suggestion of possible options for approaching this dilemma. Individual recommendations and decisions would follow a review of options with patients and their families, clearly detailing expected results and possible toxicities of various approaches within the context of an incurable illness with limited survival.

Inclusion of possible increased adverse effects of more aggressive approaches on overall quality of life must be taken into account in the overall decision making process. Assuming that patients would be offered a resection within reasonable surgical risks, patients with a good performance status and aged

65–70 should receive the standard approach of 6 weeks of RT with concurrent and adjuvant temozolomide, but may also receive a short course hypofractionated RT(\pm temozolomide). Patients aged ≥ 70 with a good performance status and a good resection could receive 6 weeks of RT with concurrent and adjuvant temozolomide, short-course hypofractionated RT or temozolomide only. Older patients with a poor performance status, particularly if bedridden, confused, and incontinent, should receive best supportive care, but in some situations (eg, a subgroup of less affected patients), short-course hypofractionated RT or temozolomide only appear to be reasonable options.

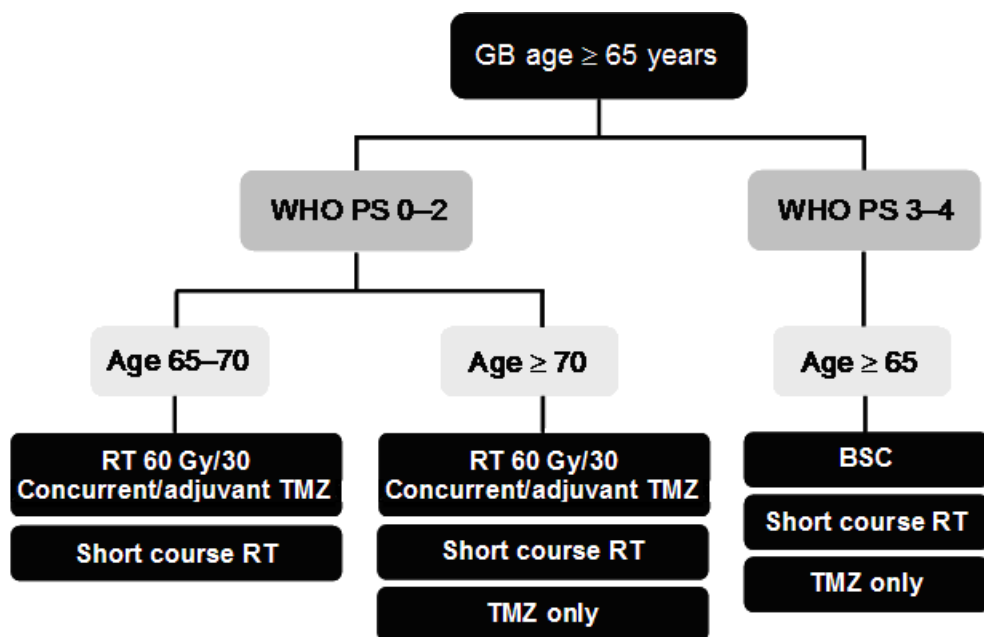
Conclusions

The management of patients with GB remains a challenge and is particularly difficult in the elderly subgroup, who currently form at least half of all patients with GB and this is soon to grow to two-thirds in the next two decades. Prognostic factors within the elderly subgroup are the same as for all patients, and the rate of methylation of the *MGMT* gene promoter appears to occur with the same frequency as in their younger counterparts. Elderly patients tolerate high dose RT and chemotherapy less well than their younger counterparts, and may benefit less from these more aggressive approaches. Until new therapies are available, it behoves us all to make the optimal use of current therapies to achieve the best survival associated with an acceptable quality of life, while utilizing limited resources in an optimal way. Currently, support of randomized phase III studies in this population remains the best way forward in examining the optimal use of currently available therapies.

Acknowledgement

Editorial assistance (formatting) was provided by Helen Varley, PhD, Evidence Scientific Solutions, Horsham, UK; this assistance was supported by Merck & Co. Inc.

Figure 1: Suggested possible options for elderly patients with GB



BSC = best supportive care; GB = glioblastoma; RT = radiotherapy; short course RT = 40 Gy/15, 30–34 Gy/10; TMZ = temozolomide; WHO PS = World Health Organization Performance Status

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